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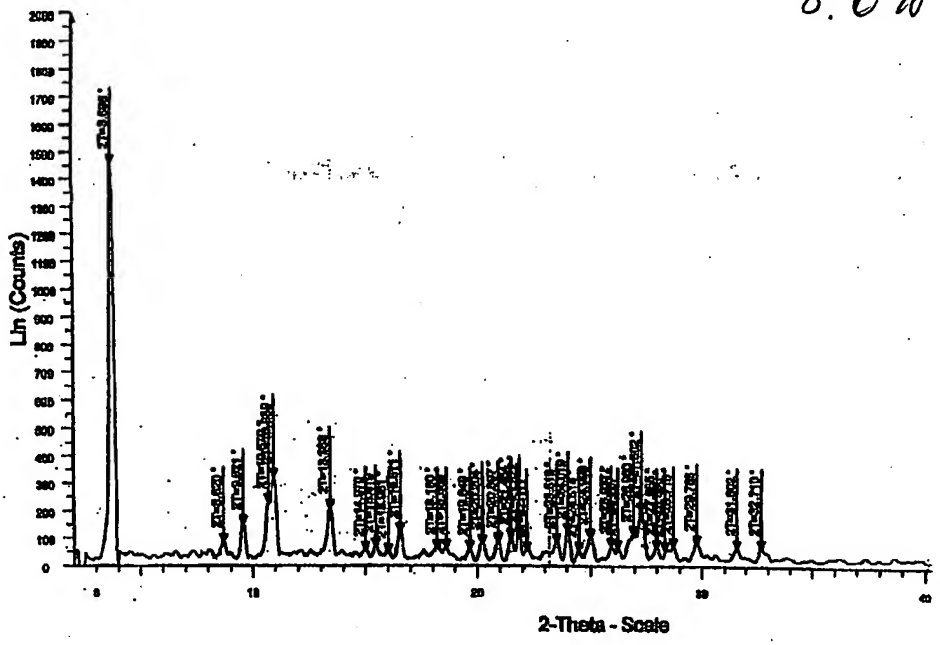
[Continued on next page]

(54) Title: NOVEL PSEUDOMORPH OF VALACICLOVIR HYDROCHLORIDE

8.6% water



(57) Abstract: The present invention relates to a stable novel pseudomorph of Valaciclovir hydrochloride and the process for its preparation by the debenzylation of 2-[(2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl N- [(benzyloxy)carbonyl]L-valinate by bubbling hydrogen gas in presence of HCl, isolating the product in a mixture of ethanol and water followed by crystallization in aq.ethanol, drying under vacuum and allowing to adsorb moisture at ambient conditions.

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report*

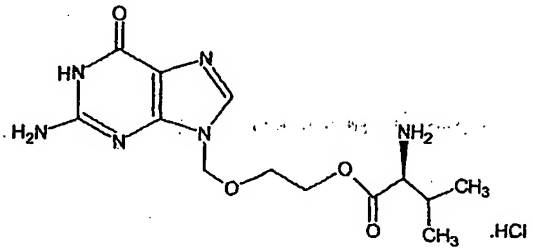
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

"Novel pseudomorph of Valaciclovir hydrochloride"

The present invention relates to novel pseudomorph of Valaciclovir hydrochloride and the process for its preparation.

Background of the Invention:

Valaciclovir hydrochloride, [2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy]ethyl L-valinate hydrochloride has the formula as given below.



Valaciclovir hydrochloride

Valaciclovir is an L-valine ester of Acyclovir. Acyclovir possesses antiviral activity and is widely used in the treatment of prophylaxis of viral infections in human beings, particularly infections caused by the herpes group of viruses. However, acyclovir is poorly absorbed from the gastrointestinal tract upon oral administration and this low bioavailability means multiple high doses of oral drug may need to be administered, especially for the treatment of less sensitive viruses or infections.

Preparation of Valaciclovir and its salts including hydrochloride salt are disclosed in U.S. Patent No. 4,957,924. The disclosed process for the preparation of valaciclovir hydrochloride monohydrate involves the condensation of CBZ-L-Valine with acyclovir in presence of 4-dimethylaminopyridine and dicyclo hexylcarbodiimide in dimethyl formamide and purification by flash chromatography yielded the intermediate 2-[(2–Amino-1,6- dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl-N-[(benzyloxy)carbonyl] L-valinate. Debenzylation of the above intermediate with 5% Pd/C catalyst in presence of 0.5 M aq. HCl, at a hydrogen pressure of 50 psi for about one day followed by removal of catalyst, concentration of the solvent afforded the white solid which was recrystallized

from water/ethanol yielded the valaciclovir hydrochloride monohydrate. The above disclosed process has the drawback of debenzylation under pressure in presence of aqueous HCl for longer time i.e. for a day. There by the process requires a special equipment to carryout the reaction under acidic and pressure conditions.

U.S. Patent No.6, 107,302 disclosed anhydrous valaciclovir hydrochloride and the process for its preparation. It further disclosed that the anhydrous valaciclovir hydrochloride has the water of hydration not more than 3.0% and characterized by its X-ray diffractions.

The PCT publication WO 03/22209 disclosed various polymorphs/ pseudomorphs of valaciclovir hydrochloride, pharmaceutical compositions containing them and the processes for preparation. The disclosed crystalline forms are form-I, form-II, form-IV, form-V, form-VI and form-VII which include valaciclovir hydrochloride monohydrate, valaciclovir hydrochloride dihydrate and valaciclovir hydrochloride sesquihydrate. The disclosed polymorphs, pseudomorphs are characterized by chemical analysis, XRD, DSC and theromogravimetric analysis. Valaciclovir hydrochloride form-I is characterized as sesquihydrate and form-IV is characterized as dihydrate. The disclosed methods used for particular embodiments are slurry method, vapour incubation method and the precipitation method.

There is a long felt need of the industry to have a process for the preparation of valaciclovir hydrochloride with out involving the special equipment during debenzylation reaction.

Summary of the invention:

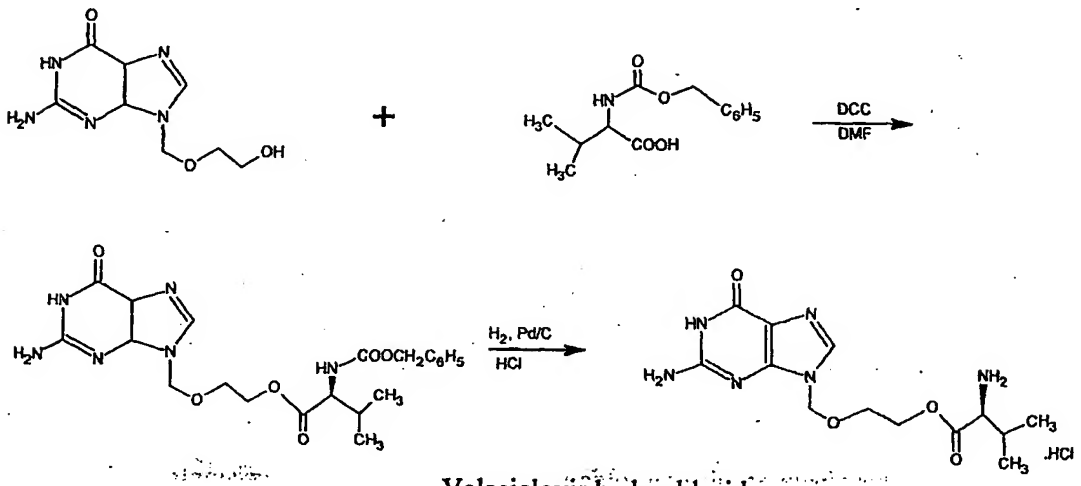
The main object of the present invention is to provide a stable novel crystalline valaciclovir hydrochloride pseudomorph.

Another object of the present invention is to provide the process for the preparation of stable novel crystalline valaciclovir hydrochloride pseudomorph.

Yet another object of the present invention is to provide a process for the preparation of valaciclovir hydrochloride without using special pressure equipment.

Accordingly in the present invention 2-[(2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl N-[(benzyloxy)carbonyl]L-valinate is debenzylated with palladium on carbon catalyst by bubbling hydrogen gas in presence of HCl,followed by filtration of catalyst, concentration and crystallization of the product in a mixture of ethanol and water. The compound is further recrystallized aq.ethanol (Scheme-1), isolation, drying under vacuum and allowing to adsorb moisture at ambient conditions affords the valaciclovir hydrochloride pseudomorph.

Scheme-1



Valaciclovir hydrochloride

The prepared valaciclovir hydrochloride pseudomorph is a novel, stable crystalline hydrate, having the water of hydration about 4.5% to about 9.5%. The valaciclovir hydrochloride pseudomorph is designated as pseudohydrate as the water present in the product is both the physically adsorbed and chemically bounded water, which is confirmed by the thermal analysis (DSC, TGA). In fact the product can be called as a cluster of valaciclovir hydrochloride pseudohydrates, characterized by its unique TGA and DSC thermograms.

Brief description of the drawings:

1. Fig.1 – XRD of valaciclovir HCl pseudomorph
2. Fig.2 – TGA of valaciclovir HCl pseudomorph
3. Fig.3 – DSC of valaciclovir HCl pseudomorph

Detailed description of the invention:

Thus in accordance with the present invention preparation of valaciclovir hydrochloride pseudomorph essentially comprises the following steps.

- Debenzylating 2-[(2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl) methoxy]ethyl N-[(benzyloxy)carbonyl]L-valinate with palladium on carbon by bubbling hydrogen gas without maintaining the pressure in presence of HCl
- Removing the catalyst followed by removal of solvent
- Crystallizing the product from ethanol - water
- Dissolving the isolated solid in water
- Removing insolubles if any
- Adding ethanol to the clear solution
- Isolating the precipitated product
- Drying the wet cake under vacuum followed by allowing the product to absorb the moisture in ambient conditions

2-[(2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl) methoxy] ethyl N-[(benzyloxy)carbonyl]L-valinate is suspended in a mixture of methanol and THF, 5% palladium on carbon or 10% palladium on carbon catalyst is added and hydrogen gas is bubbled through the reaction mass at a temperature of about 10°C to about 45°C preferably at 20°C to 35°C for about 45 min to 8 hrs. Catalyst is removed, THF and methanol mixture is distilled off under vacuum at temperature below 60°C. Ethanol is added and adjusted the water content of the reaction mass to about 15% to about 35%

preferably about 20% to about 30%. The temperature of the reaction mass is raised to about 40 to 45°C to get a solution, cooled the reaction mass to a temperature of 5°C to 30°C.The precipitated valaciclovir hydrochloride is isolated which can be further recrystallized as follows.

Wet valaciclovir hydrochloride is dissolved in water at temperature of about 25°C to about 65°C, insolubles are removed (if any), ethanol is added and the reaction mass is cooled to a temperature of 20°C to 30°C, precipitated product is isolated and the wet cake is dried at temperature of about 45°C to about 55°C under vacuum for about 6 to 18 hrs (till the ethanol content comes to about 2 to 4 %) and then dried at room temperature (Allowed to adsorb / absorb moisture upto a level of about 8 % to 9.5%) for about 4 to 6hrs afforded the valaciclovir hydrochloride pseudomorph.

2-[(2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl- N-[(benzyloxy)carbonyl]L-valinate is prepared by the prior art methods.

The invention is further illustrated with the following example

Example: Preparation of valaciclovir hydrochloride pseudomorph.

Step-1:-

100g of 2-[(2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy] ethyl] N-[(benzyloxy) carbonyl]L-valinate is suspended in mixture of THF (1320 ml), methanol (1320 ml) and 240 ml of 0.5M aqueous hydrochloric acid is added. Reaction mixture maintained for about 15 min to get a clear solution. 10 g of 10% Palladium on carbon catalyst is added to the reaction mixture and hydrogen gas is bubbled into the reaction mass for about 3 hrs at temperature of 25°C - 30°C. The catalyst is filtered, washed the catalyst with 100 ml of 1:1 mixture of THF, methanol, combined the filtrate, washings and distilled off the solvents under vacuum at temperature of below 60°C. 300 ml of ethanol is added to the reaction mass and adjusted the moisture content to 23% by addition of ethanol. The reaction mass is cooled to 25°C–30°C, mixed for about 30 min and the temperature is raised to 40°C–45°C. Reaction mass is mixed for about 30 min at 40°C–45°C, slowly

cooled to 20°C and mixed for about 1 hr at 20°C–25°C. The precipitated product is filtered, washed the wet cake with 50 ml of chilled ethanol.

Weight of the wet cake is 90g.

Step-2:-

The wet cake (90 g) obtained in the above step is suspended in 100 ml DM water and the temperature is raised to 50°C–55°C, mixed for about 15 min at 50°C – 55°C and filtered the solution through hyflow bed to remove insolubles. Filtrate is cooled to 40°C-45°C, 340 ml ethanol is added at temperature of 40°C–45°C and cooled the reaction mass to 20°C–30°C. Reaction mass is mixed for about 15 min and the temperature is raised to 35°C–45°C,maintained for about 15 min at 35°C-45°C, cooled to 20°C– 25°C and maintained for about 30 min at 20°C–25°C.The precipitated product is filtered, washed the wet cake with 50 ml of chilled ethanol and dried at 50°C–55°C under vacuum for about 12 hrs (ethanol content is 2.3%. The material is further dried at 25°C–35°C (allowed to absorb the moisture content) for 4 hrs (till the moisture content becomes 8.6%).

The dry weight of valaciclovir hydrochloride pseudomorph is 45 g.

Moisture content: 8.6%

The typical XRD, TGA and DSC are as shown in Fig.1 to Fig.5

We claim:

1. A process for the preparation of valaciclovir hydrochloride pseudomorph comprising steps

- Debenzylating 2-[(2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl) methoxy]ethyl N-[(benzyloxy)carbonyl]L-valinate with palladium on carbon by bubbling hydrogen gas without maintaining the pressure in presence of HCl
- removing the catalyst followed by removal of solvent
- crystallizing the product from ethanol - water
- dissolving the isolated solid in water
- removing the insolubles (if any)
- adding ethanol to the clear solution
- isolating the precipitated product
- drying the wet cake under vacuum followed by allowing the product to absorb the moisture in ambient conditions

2. A process as claimed in claim 1, wherein hydrogen gas bubbling is at temperature of 10°C to 45°C.

3. A process as claimed in claim 1, wherein the palladium on carbon catalyst is either 5% or 10% w/w.

4. A process as claimed in claim 1, wherein the hydrogen gas bubbling is for about 45 min to 8 hrs.

5. A process as claimed in claim 1, wherein the solvent is removed under vacuum at temperature of below 60°C.

6. A process as claimed in claim 1, wherein product is crystallized from ethanol having the moisture content about 12% to 30% and more preferably about 20% to 30%.

7. A process as claimed in claims 1, wherein drying is performed at temperature of 50°C–55°C under vacuum.

8. A process as claimed in claim 1, wherein the product is allowed to absorb moisture up to 9.5%.

9. Crystalline valaciclovir hydrochloride psuedomorph.

10. Crystalline valaciclovir hydrochloride pseudomorph as claimed in claim 9, wherein characterized by having x-ray diffractogram as shown in Fig.1

11. Crystalline valaciclovir hydrochloride pseudomorph as claimed in claims 9, wherein characterized by showing the DSC endotherms as shown in Fig 3-5.

12. Crystalline valaciclovir hydrochloride pseudomorph as claimed in claims 9 to 11, having the moisture content about 4.5% to about 9.5%.

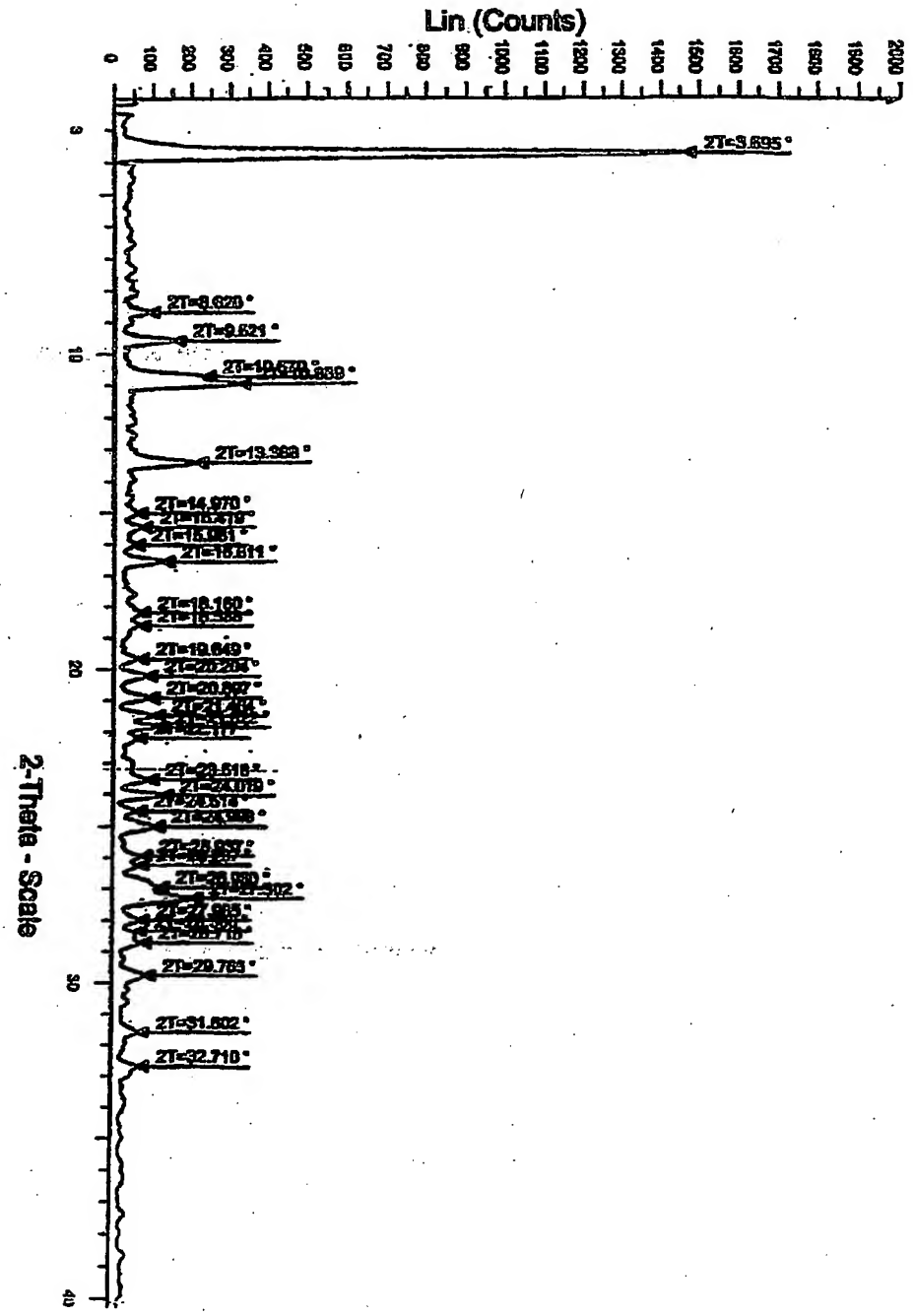

Lin (Counts)
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
2000
2-Theta - Scale
3
10
20
30
40
2T=8.695°
2T=9.620°
2T=9.621°
2T=13.368°
2T=14.970°
2T=16.811°
2T=18.160°
2T=19.649°
2T=29.783°
2T=31.602°
2T=32.710°

Figure-1

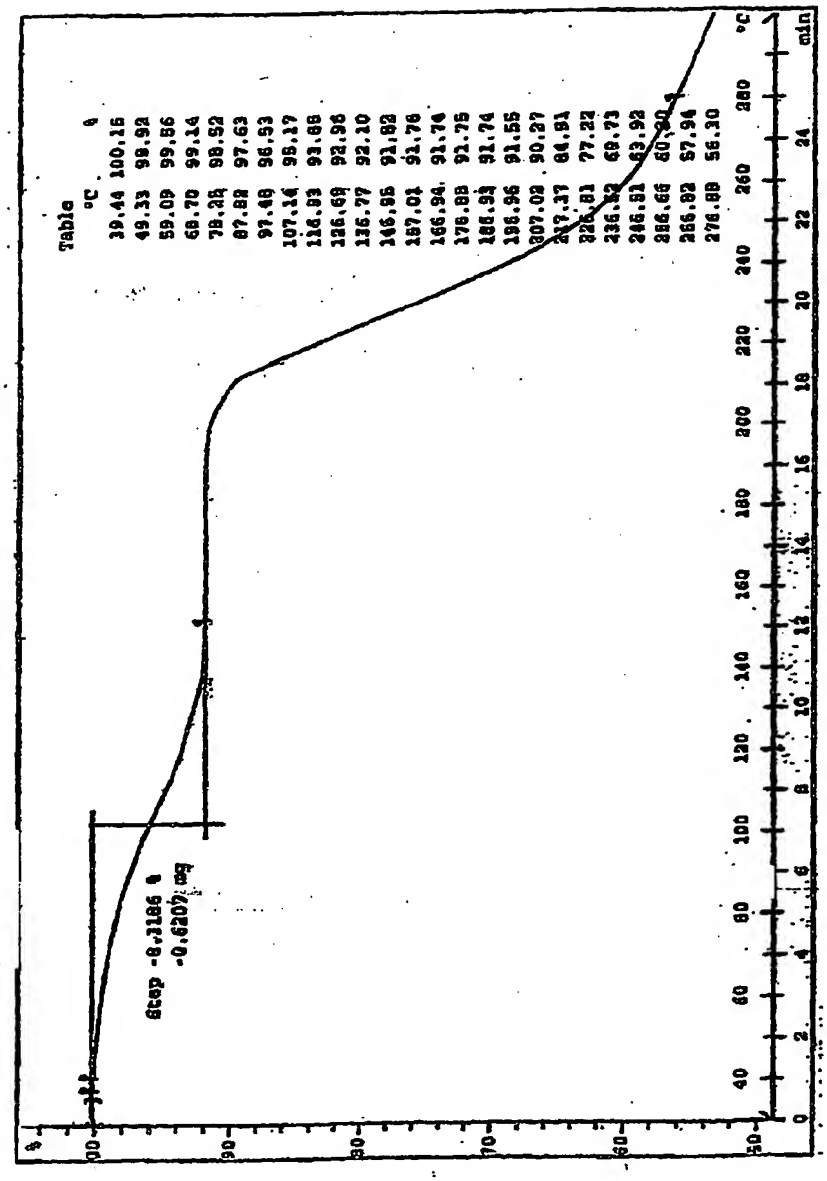


Table
°C %
39.44 100.16
49.33 98.92
59.09 99.86
68.70 99.14
78.28 98.52
87.88 97.63
97.48 96.93
107.14 96.17
116.83 93.88
126.69 92.96
136.77 92.10
146.95 91.82
157.01 91.76
166.94 91.74
176.88 91.75
186.93 91.74
196.96 91.55
207.03 90.27
217.37 84.91
226.81 77.22
236.52 68.73
246.81 63.92
256.66 60.20
266.82 57.94
276.88 56.30
Step -8.3186 %
-0.6207 mg
%
°C
min

Figure-2

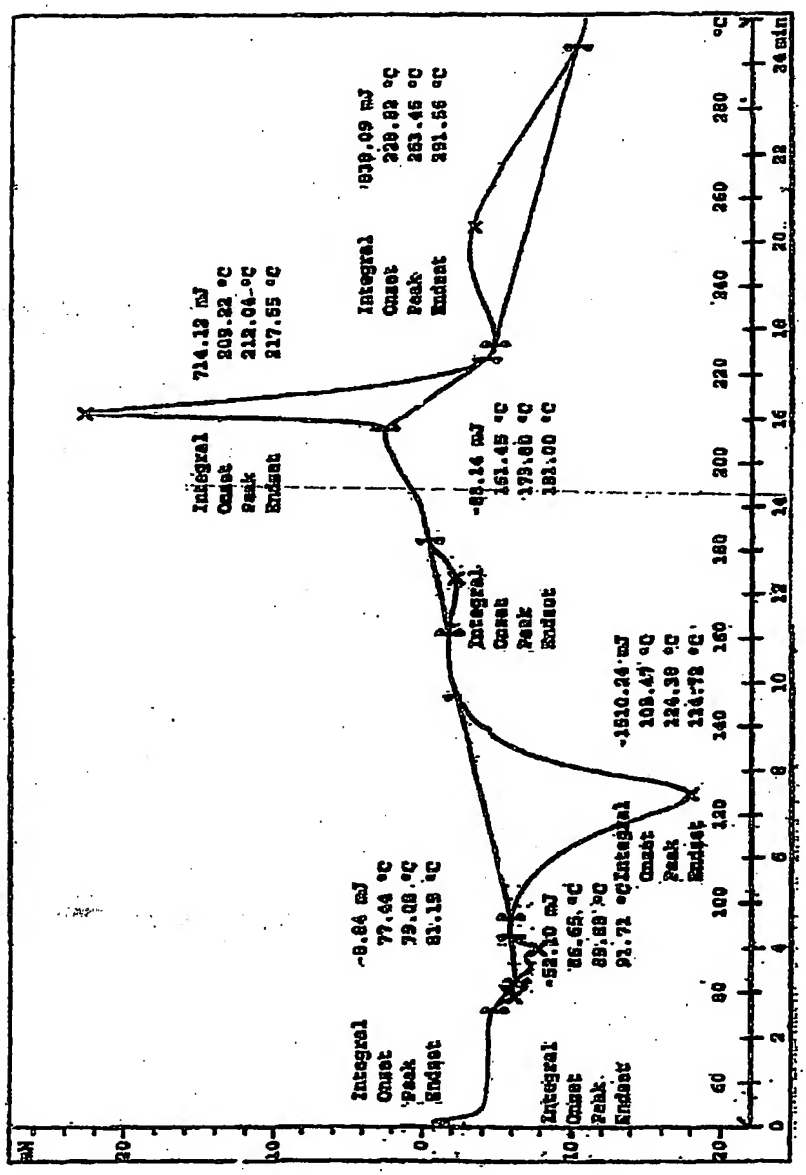

Integral 714.12 mJ
Onset 209.22 °C
Peak 212.06 °C
Endset 217.55 °C
Integral -8.84 mJ
Onset 77.44 °C
Peak 79.08 °C
Endset 81.19 °C
Integral -53.10 mJ
Onset 86.65 °C
Peak 88.88 °C
Endset 92.71 °C
Integral -88.14 mJ
Onset 161.45 °C
Peak 179.80 °C
Endset 181.00 °C
Integral -1510.24 mJ
Onset 108.47 °C
Peak 126.38 °C
Endset 134.78 °C
Integral 1838.09 mJ
Onset 228.82 °C
Peak 253.46 °C
Endset 281.56 °C
mW
min
°C

Figure-3

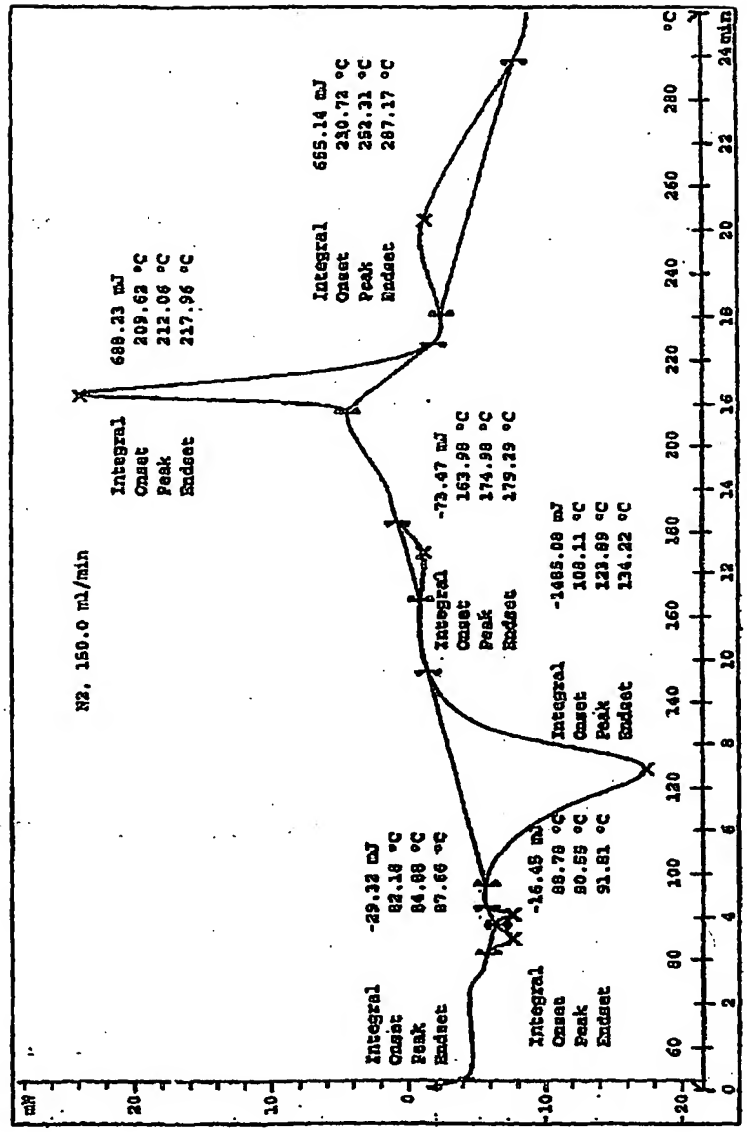

N2, 150.0 ml/min
Integral 689.23 mJ
Onset 209.62 °C
Peak 212.06 °C
Endset 217.96 °C
Integral 665.14 mJ
Onset 210.72 °C
Peak 252.31 °C
Endset 287.17 °C
Integral -73.47 mJ
Onset 163.98 °C
Peak 174.98 °C
Endset 179.29 °C
Integral -1465.08 mJ
Onset 108.11 °C
Peak 123.89 °C
Endset 134.22 °C
Integral -29.32 mJ
Onset 82.18 °C
Peak 84.88 °C
Endset 87.66 °C
Integral -16.45 mJ
Onset 88.78 °C
Peak 90.59 °C
Endset 91.81 °C
mW
°C
24 min

Figure-4

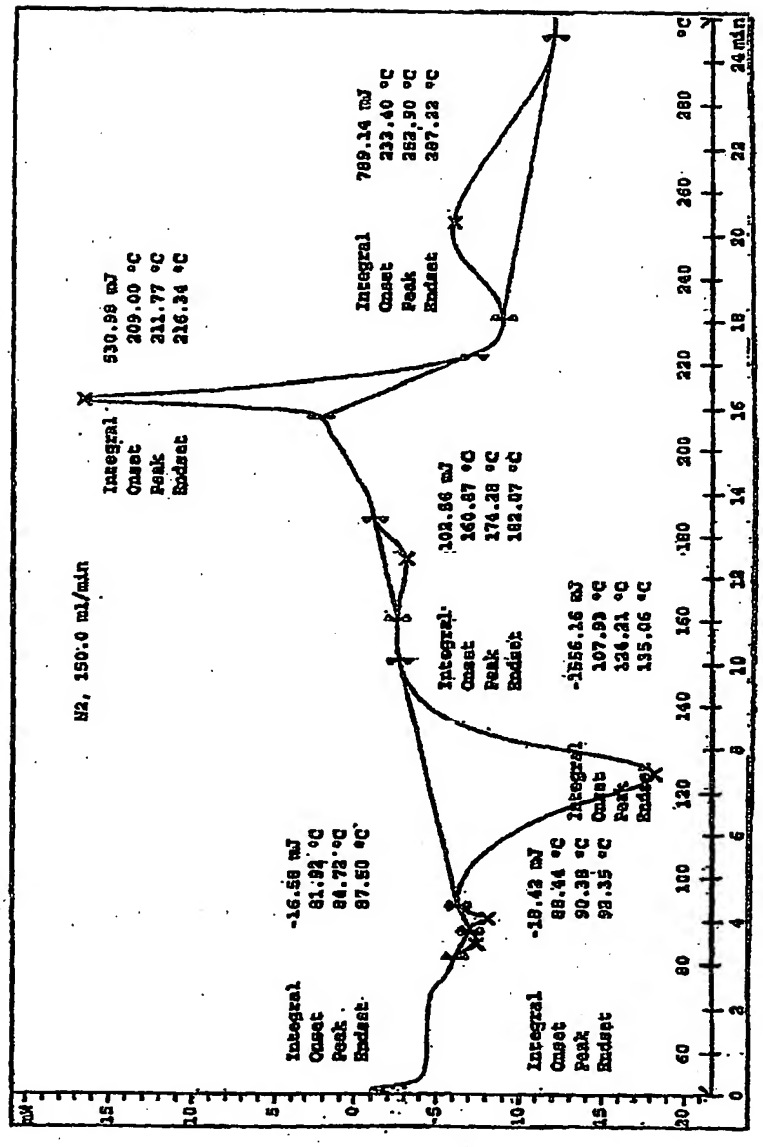

N2, 150.0 ml/min
Integral 530.98 mJ
Onset 209.00 °C
Peak 211.77 °C
Endset 216.34 °C
Integral 789.14 mJ
Onset 233.40 °C
Peak 252.90 °C
Endset 287.22 °C
Integral 102.86 mJ
Onset 160.87 °C
Peak 174.28 °C
Endset 182.07 °C
Integral -1556.16 mJ
Onset 107.93 °C
Peak 124.21 °C
Endset 135.06 °C
Integral -16.58 mJ
Onset 81.92 °C
Peak 84.72 °C
Endset 87.50 °C
Integral -18.42 mJ
Onset 88.14 °C
Peak 90.38 °C
Endset 93.35 °C
mW
°C
min

Figure-5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2005/000270

A. CLASSIFICATION OF SUBJECT MATTER
IPC[7]: C07D 473/18, A61K 31/522
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC[7]: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
—

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPI, PAJ, EPODOC, REGISTRY, CAPLUS,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2003/022209 A2 (TEVA PHARMACEUTICAL INDUSTRIES LTD.), 20 March 2003 (20.03.2003) *the whole document, esp. pages 3-4, 16-23, claims, figures.* —	1-8
X	EP 308 065 A2 (THE WELLCOME FOUNDATION LIMITED), 22 March 1989 (22.03.1989) *the whole document, esp. 3, 4, examples, claims.* —	1-8
P,A	WO 2005/000850 A2 (TEVA PHARMACEUTICAL INDUSTIRES LTD.), 6 January 2005 (06.01.2005) *the whole document, esp. pages 3, 4,7,9-14, claims, figures.* —	1-8

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 November 2005 (08.11.2005)	17 November 2005 (17.11.2005)
Name and mailing address of the ISA/ AT **Austrian Patent Office** Dresdner Straße 87, A-1200 Vienna Facsimile No. +43 / 1 / 534 24 / 535	Authorized officer WENIGER S. Telephone No. +43 / 1 / 534 24 / 341

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2005/000270

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 2004/106338 A1 (EOS ECZACIBASI OZGUN KIMYASAL URUNLER SANAYI VE TICARET A.S.), 9 December 2004 (09.12.2004) *the whole document, esp. claims, figures.*	1-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2005/000270

Continuation of first sheet

Continuation No. II:

Observations where certain claims were found unsearchable

(Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 9-12 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The chemical compound claimed in claim 9 ("crystalline valaciclovir hydrochloride pseudomorph") is not sufficiently characterized due to the lack of any characteristic features given for the (new) crystalline and/or "pseudomorphic" nature of the known chemical compound. Since the giving of a certain moisture content does not make any contribution to a clear and concise characterization of the compound "crystalline valaciclovir hydrochloride pseudomorph", the subject matter of claim 12 is not sufficiently defined, as well.

Claims 10 and 11 refer to parts of the description (figures), only, and do not comprise any charasteristic inventive technical features.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN 2005/000270

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP A 308065		GR T3 3020372T	1996-09-30
		NL I1 960001I	1996-03-01
		KR B1 9604940	1996-04-18
		CY A 1833	1995-12-01
		HK A 39595	1995-03-24
		SG A2 9590337	1995-09-01
WO A 2003022209		none	
WO A1 2004106338	2004-12-09	AU A1 2003232719	2005-01-21
WO A2 2005000850	2005-01-06	US A1 2005085491	2005-04-21